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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

4/18/05 RA

Office Action Summary	Application No.	Applicant(s)	
	10/058,291	HARTLEY ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,38-66,69-75,77 and 79-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-36,38-66,69-75,77 and 79-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a request for continued examination. Where applicable, a response to Applicant's arguments is set immediately following the body of any rejections repeated herein. Claims 35-36, 38-66, 69-75, 77 and 79-112 are under consideration in this action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/24/2005 has been entered.

Information Disclosure Statement

The information disclosure statements (IDSs) filed 02/18/2005 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. First, on page 1 of the Sixth Supplemental IDS, two foreign language documents are cited, where an English translation for the same is not present in the record. Second, on pages 2-3 of the Fourth Supplemental IDS, various links to internet sites are not considered, because the listings do not meet the requirements as set forth 37 CFR 1.98, i.e., a copy of the page(s) accessed must be provided. Third, the documents on the Fifth Supplemental IDS are not publishable. The documents have been considered but are crossed through because they are not publishable. The IDSs has been placed in the application file, but the information referred to therein has not been considered as to the merits.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claim 39-66, 79-96 and 101-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Applicants' assertion that the terms, "recombination site" and "cloning site" are not vague and indefinite is not deemed persuasive. (See infra, Response to Arguments, immediately following the body of this rejection). Claims 39, 43-45, 52, 55-56 and 58-60 recite the limitation "recombination site". The term does not appear to be explicitly defined in the instant specification. This term is vague and indefinite in that it is unclear if the term is meant to encompass literally any nucleic acid that might serve as a site for a recombination (e.g. homologous, non-homologous recombination, any sequence used in PCR cloning etc.) or is meant, as appears to be the case upon reading the specification, a site-specific recombination sequence?

Dependant claims drawn to nucleic acids *comprising* site-specific sequences (e.g. loxP) remain vague and indefinite, because such nucleic acids may contain sequences at the recombination site in addition to the site-specific sequence.

Claim 47 and 62 recite the limitation "one cloning site". The term does not appear to be explicitly defined in the instant specification. The term is vague and indefinite in that it is unclear what the term encompasses. Does applicant intend that the term be drawn to recombination sites or a single restriction enzyme site?

Response to Arguments

Applicants' arguments filed 01/24/2005 (Remarks) have been fully considered but they are not persuasive. Applicants assert that one of ordinary skill in the art would readily understand that "recombination site" refers to a site-specific recombination site. (Remarks, pp. 19-20). In essence, the issue is whether the limitation "recombination site" exclusively translated to mean "site specific recombination site"?

Applicants are required to particularly point out and distinctly claim their invention, but by claiming a critical structural element in an ambiguous fashion the claims fail said requirement. Therefore the answer to the question of whether the term "recombination site" means "site-specific recombination site" must be no. This is so, because the term "recombination site" is not specifically defined in the specification and one of skill in the art will recognize that the term "recombination site" can have several interpretations, each of which impart patentably distinguishable characteristics in regard to compositions comprising said recombination site.

For example, if a recombination site is interpreted to mean a site that contains sequences necessary for homologous recombination, then the sequences as well as size of the fragment comprising the sequences are critical elements for whether homologous recombination will occur. However, such critical structures need not be considered where the recombination site is interpreted to mean "site-specific recombination". In other words, it would be remedial to replace "recombination site" with "site specific recombination site".

Applicants point out to various portions of the specification that discuss or describe *site-specific recombination*, for support of the assertion that the term "recombination site" is not vague and indefinite. (Remarks, p. 19; pointing to passages in the Specification, at pp. 26-30). The passages to which Applicants point discuss site-specific recombination, but the specification on whole or the passages cited do not exclusively delimit the limitation "recombination site" to mean site-specific recombination (e.g., the limitation could mean a sequence for PCR cloning or a sequence homologous recombination). As a term of art, "recombination site" does not automatically signal to one of ordinary skill in the art that the particular site is involved is exclusively a site-specific recombination.

With respect to dependent claims directed to nucleic acids comprising site-specific recombination sequences (e.g., loxP), Applicants refer to arguments made in the previous reply. In addition, Applicants assert that merely because additional sequences occur at the recombination site do not render said claims vague or indefinite. (Remarks, p. 20, ¶ 1). However, as stated above, if such additional nucleic acid sequences are present at the site-specific recombination site then the metes and bounds of the claimed compositions would be interminable, because any sequence can relate homologous recombination.

As stated above, it would be remedial to replace "recombination site" with the term "site-specific recombination site".

With respect to the term, "on cloning site" being vague and indefinite, Applicants refer to arguments made previously in referring to Figure 3D and the corresponding description in the specification, for support of the assertion that two site-specific recombination sites flank a multiple cloning site. (Remarks, p. 20, last ¶). In addition, Applicants assert that the limitation "one cloning site" is a "single cloning site" and multiple such sites make up a "multiple cloning site". The issue is whether "a cloning site" exclusively means a "multiple cloning site" as is contemplated in Figure 3D? The answer is no, because "a cloning site" can be virtually any sequence (e.g.., 15 base pair sequence used in PCR cloning), but a "multiple cloning site" is a term of art that one of skill will recognize to mean a "a cloning site" comprising multiple restriction sites.

Put another way, to assert that "a multiple cloning site" means multiples of "a cloning site" actually results in further ambiguity (e.g., multiple 15bp sequences used in PCR cloning). In sum, the claims are not directed to "a restriction site" or a "multiple cloning site" comprising multiple restriction sites, as Applicants appear to be arguing. In sum, for reasons of record and further stated herein, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 52-66, 87-91 and 101-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

This rejection was made previously and is repeated herein. A response to Applicants' arguments is included below. (infra, Response to Arguments). The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The broadest claim is drawn to a nucleic acid comprising a functional antibiotic resistance gene, where *any* recombination site separates a first and second portion of the antibiotic resistance gene. The recombination site can reasonably be interpreted to comprise *any* site from *any* source and be of *any* type. Notwithstanding the separation of the two portions by a recombination site, the nucleic acid comprises a functional antibiotic resistance gene.

Even in the most specific embodiments, the first portion of the antibiotic resistance gene is a promoter sequence and the recombination site is a lox or att site or mutants thereof. Therefore a recombination sequence comprising some sequence from lox or att (e.g. mutant) would satisfy the claim limitation. Additionally, the lox site can be a loxP site. A reasonable interpretation of the term "loxP" is that it can be read broadly to encompass any functional variant of loxP that can be specifically recombined by the Cre recombinase (e.g. having the requisite Cre binding site). Therefore, the rejected claims encompass an enormous genus of nucleic acids that comprise a functional antibiotic resistance gene, notwithstanding the intervening recombination site sequences.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The teachings of the specification appear to be limited to site-specific recombination sites utilized in a technique for recombination cloning wherein the first portion of antibiotic resistance gene (e.g. Kanamycin; "Km") comprises a regulatory sequence (e.g. repressor-specific binding site) and the second portion is the Km gene, each separated from the other by a site-specific recombination site, so that when the repressor binding site and repressor are present, then cells containing the Km gene remain sensitive to the antibiotic. (Spec. p. 44, Example 5).

The specification does not provide a basis for the skilled artisan to envision other embodiments of the claimed invention wherein the nucleic acid encoding a functional antibiotic resistance gene, comprises a first portion and second portion separated by *any* recombination site sequence. For example, most of the rejected claims encompass embodiments where the nucleic acid simultaneously comprises a site-specific recombination site (e.g. LoxP) inserted into a protein coding sequence such that the nucleic acid encodes a functional protein and is capable of site-specific recombination.

Given the enormous breadth of the nucleic acids encompassed by the rejected claims, and given the limited description from the instant specification of such nucleic acids, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to

describe the broadly claimed genus of nucleic acids. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments

The issue is whether the specification discloses a sufficient number of embodiments for the genus of nucleic acids claimed? An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966). Applicants' assertion that the specification provides sufficient basis for the ordinary skilled artisan to envision embodiments of the claimed invention is not deemed persuasive.

Applicants point to remarks filed previously (Reply, filed June 24, 2004), where Applicants assert that the Examiner has provided no evidence that the various recombination sites discussed in the specification would in any way alter or preclude the practice of the presently claimed invention. (Remarks, p. 17, ¶ 1). Applicants are reminded that this assertion is relevant to an enablement rejection not a written description rejection.

In addition, Applicants point to several passages in the specification where numerous "site-specific recombination" systems are disclosed. (Remarks, p. 16, middle ¶; noting in the Specification, pp. 14 and 22-30). Furthermore, Applicants point to Figures 4A-4C, Example 5, for additional non-limiting examples of nucleic acid molecules comprising site-specific recombination sites (i.e., *att* and *lox* sites). (Remarks, p. 16, last ¶).

In sum, Applicants' argument amounts to the assertion that disclosing several "site-specific recombination sites" is a sufficient disclosure of embodiments for the genus of nucleic acids encompassing *any* recombination site.

As stated in the previous action, the examples and discussions in the specification are directed to site-specific recombination, but the claims are broadly drawn to any recombination site. (e.g. Spec. p. 14, ll. 1-15; p. 17, ll. 1-12; pp. 22-30). In addition, as pointed out previously, a reasonable interpretation of claims is that one of skill would have to envision any functional variant of the particular site-specific recombination sites disclosed. Therefore, the nucleic acids of the invention comprise undisclosed nucleic acid sequences or fragments thereof that are involved in *any* recombination (e.g., homologous recombination).

It follows that there is a high level of unpredictability with respect to the nucleic acid structures claimed as functioning in any recombination event, in the context that correlate to the functionality of any recombination event. In other words, the limitation "recombination site" encompasses structures other than the site-specific recombination sites, for which there is ample disclosure. Therefore, it is not incorrect to state that Applicants do not sufficiently describe a sufficient number of embodiments for other structures involved in recombination, exclusive of site-specific recombination.

Moreover, the rejected claims encompass an enormous genus of nucleic acid molecules that comprise a functional antibiotic resistance gene, in addition to the genus of intervening recombination site sequences. For example, depending on the intervening sequence, recombination can result the two antibiotic regions forming a less than full-length gene, thus encoding a nonfunctional antibiotic (e.g., where intervening sequences are involved in

homologous recombination). Based on the instant disclosure one cannot envisage a sufficient number of embodiments of nucleic acid structures comprising *any* recombination site.

As the Guidelines for Written Description state:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art", furthermore, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105).

In the instant case, the genus encompasses the critical limitation of all "recombination sites", but the disclosure is limited to "site-specific recombination sites". In sum, for reasons of record and stated herein, the full disclosure does not provide sufficient disclosure for one of skill to envisage a sufficient number of embodiments within the claimed genus of nucleic acid sequences.

3. Claims 35-36, 38-66, 69-75 and 79-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

This rejection was made in the previous action. A response to Applicants' arguments immediately follows the body of this rejection. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, all independent claims recite the limitation, "immediately adjacent", which does not have literal support in the specification.

Applicants point to several different passages in the specification, however none of these passages or any other passages appear to contain support for said limitation. Therefore, the **limitation, "immediately adjacent" is deemed NEW MATTER**.

Response to Arguments

Applicant's arguments filed 01/24/2005 have been fully considered but they are not persuasive. Applicant asserts that exemplary support is present in the specification to show that the recombination sites and the related genes, portions of genes, etc., have no intervening nucleotides between them. (Remarks, p. 21, bottom ¶). Applicants more particularly point to Figures 4C, 8B, 8I and 8J for support.

Figure 4C depicts a schematic that illustrates a vector schematic, where an arrow designating an SP6 promoter occurs next to a small triangle designating a *lox*P site. However, in examining this schematic it is impossible to deduce whether the two structures are "immediately adjacent" without any intervening sequence.

Furthermore, one is inclined to believe that there are intervening sequences considering that Applicants' reply controverts the assertion that no intervening sequences are present. For example, where Applicant states, "the nucleic acid molecules of the present invention can comprise, and often will comprise, nucleotide sequences at the recombination site in addition to the site-site specific recombination sites." (Remarks, p. 20, ¶ 1). In any event, without a sequence map of the vector depicted in Figure 4C, it is impossible to know whether intervening sequences are present. Therefore, whether Applicants have implicit support in lieu of explicit literal support is indeterminable, where the limitation "immediately adjacent" encompasses a genus of sequences with a particular structural limitation.

Additional figures 8B, 8I and 8J suffer the same infirmity, with respect to whether they demonstrate implied support for the limitation "immediately adjacent". In sum, for reasons of record and further stated herein, the rejection is maintained.

Claim Rejections - 35 USC § 102

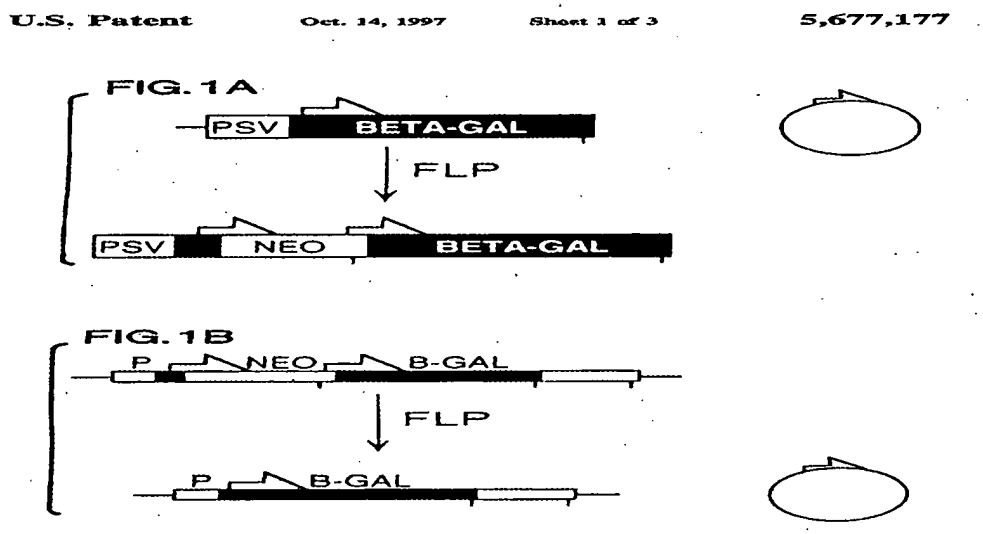
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. **Claims 39, 43, 47-49, 52-54, 58, 62-64, 79, 81, 87-88, 90, 101-102 and 104-105 are rejected under 35 U.S.C. 102(e) as being anticipated by Wahl et al. (US 5,677,177; see entire document; hereinafter the '177 patent).**

The limitation "immediately adjacent" is interpreted to mean one structure is next to another structure, such as depicted in instant drawing 4C. However, the limitation is not interpreted to mean that there are no intervening sequences necessarily. Furthermore, the limitations "first" and "second portion" of an antibiotic gene are interpreted as broadly as reasonable to include a promoter operably linked (i.e., driving transcription) of an antibiotic gene. Vector or expression vector is interpreted to mean any structure comprising the transcription units/elements.

The '177 patent teaches a site-specific recombination-mediated gene modification process. More particularly, the reference teaches nucleic acid molecules that contain a site-specific recombination site (i.e., FLP target sites). (e.g., col. 8, Example 1). Furthermore, the nucleic acid molecule can have more than one of said recombination sites. (e.g., Fig. 2A; col. 8, l. 58). Attention is directed to the figures section of the '177 patent:

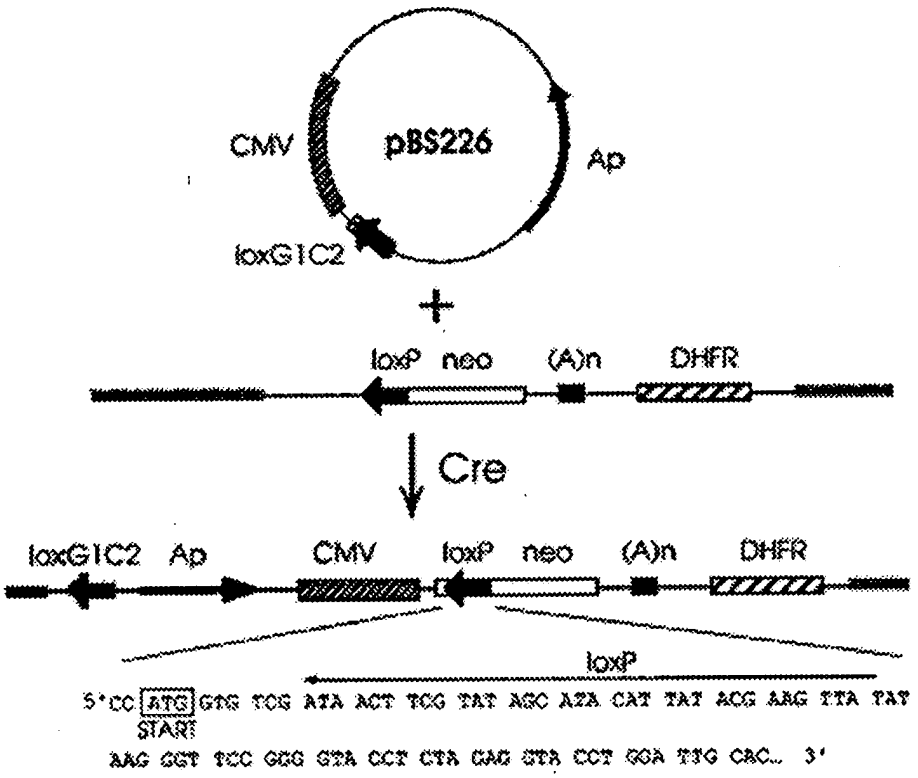


As is clearly observed in Figures 1A or 1B, a promoter element (i.e., P or PSV) is separated from an antibiotic resistance gene (i.e., "NEO" for neomycin). Furthermore, either the promoter or the antibiotic resistance gene is "immediately adjacent" to at least a site-specific recombination site, i.e., half-arrows designating *FLP* sites. (e.g., col. 8, l. 58). The nucleic acid molecules contain two *FLP* sites. (Id.). Furthermore, nucleic acid molecules are vectors or more particularly expression vectors, because they are transfected into host cells to observe phenotypic changes. (e.g., col. 9 to col. 10, Table 1; col. 11 Example 2, bridging to Col. 12, Example 3). Therefore the '177 patent anticipates the rejected claims.

5. **Claims 35-36, 38-49, 52-64, 69, 72, 75, 79-82, 8791, 97, 99, 101-102104-105, 107-108, 110-111 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukushige et al. (Proc. Natl. Acad. Sci. 1992; Genetics; 89:7905-9; see entire document).**

The claims are interpreted consonant with what is stated above. Additional claims delimit the site-specific recombination site to *lox*P.

Fukushige et al. teach nucleic acid molecules involved in site-specific recombination. More particularly, attention is directed to p. 7906, Figure 2:



As is clearly observed, at least a single *lox*P site is present "immediately adjacent to an antibiotic gene (i.e., neo), and a promoter (i.e., CMV) is separated by said *lox*P from the *neo* gene. Furthermore, two *lox* sites are present on the expression unit (i.e., expression vector) .

In addition, CHO cells are transfected with or contain said expression vector. (e.g., p. 7905, col.2). In sum, Fukushige et al. anticipate the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 35-36, 38-66, 69-75, 77 and 79-112** are **rejected under 35 U.S.C. 103(a) as being unpatentable over Fukushige et al. and Wahl et al. (US 5,677,177) and further in view of Lenski et al. (J. Bact. 1994; 176: 3140-47; reference of record).**

The claims are interpreted consonant with the interpretations stated above. Furthermore, the '177 patent and Fukushige et al. are applied herein to the claims as stated above. (supra, Rejections, No. 4 and 5).

Additional claims delimit the antibiotic resistance gene to chloramphenicol and the host cell as bacterial, i.e., *Escherichia coli*.

Fukushige et al. do no explicitly teach that chloramphenicol as the antibiotic gene, nor that bacterial cells are host cells.

The '177 patent doesn't explicitly teach that chloramphenicol is the antibiotic gene, nor that bacterial cells are host cells. However, the '177 and Fukushige et al. both teach nucleic acid molecules and host cells where *FRT* and *lox*P are the site-specific recombination sites. Furthermore, the '177 patent teaches that in methods of recombination between nucleic acid molecules comprising site-specific recombination sites (i.e., FLP), genes that can be operably linked to said recombination sites can be any selectable markers or genes for antibiotic resistance, relative to the phenotype of the recipient cells. (e.g., col. 6, ll. 37-47). Therefore, the '177 patent provides motivation to one of skill in the art to utilize the nucleic acid molecules and recombination system while utilizing additional antibiotic genes and recipient cells.

Lenski et al. teach several different antibiotic resistance genes that can be used as selection markers and to enhance bacterial fitness in one of the most widely studied and utilized bacterial species – *E. coli*.

Therefore, it would have been obvious to use a host of different antibiotic genes, such as chloramphenicol, in the expression vectors that are taught by Fukushige et al. and the '177 patent so as to extend the range of antibiotic resistance genes. In addition it would have been obvious to use a recipient cell- such as *E. coli*, in which a particular antibiotic resistance gene, such as chloramphenicol will relate to a phenotypic selection.

One would have been motivated to use different antibiotic genes and different host cells to obtain the benefit of an extended range of antibiotics and to use widely available and easily propagated cells. Given the level of skill at the time of invention, there would have been a reasonable expectation of success in modifying the expression vectors taught by Fukushige et al. with a chloramphenicol antibiotic resistance gene and to utilize said vector in an appropriate recipient cell, such as *E. coli* as is suggested by the '177 patent.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER